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EXAMINER	
HUYNH, PHUONG N	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 04/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/803,918	DAYER ET AL.	
	Examiner	Art Unit	
	Phuong Huynh	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-16 and 18-61* is/are pending in the application.

4a) Of the above claim(s) *1-8,11-14,18-35,44,45 and 50-61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,10,15,16,36-43 and 46-49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 September 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-16 and 18-61 are pending.

2. Claims 1-8, 11-14, 18-35, 44-45, and 50-61 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. Claims 9-10, 15-16, 36-43, and 46-49 are being acted upon in this Office Action.

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 9-10, 15-16, 36-43 and 46-49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for

(1) A process for making an apo-A-I fragment T-cell activation inhibitor-like polypeptide fragment comprising culturing a eukaryotic cell comprising a vector comprising a nucleic acid molecule consisting of the nucleotide sequence selected from the group consisting of: (a) the nucleotide sequence as set forth in residues 73 to 582 in SEQ ID NO: 1; (b) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 194 in SEQ ID NO: 2; (c) the nucleotide sequence as set forth in residues 73 to 432 in SEQ ID NO:1; (d) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 144 in SEQ ID NO:2; (e) the nucleotide sequence as set forth in residues 466 to 801 in SEQ ID NO:1 ; (f) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 113 in SEQ I D NO:2; (g) a nucleotide sequence encoding the polypeptide as set forth in residues 73 to 113 in SEQ ID NO:2; (h) a nucleotide sequence encoding the polypeptide as set forth in residues 156 to 267 in SEQ ID NO:2 wherein the polypeptide inhibits tumor necrosis factor (TNF) or interleukin-1 (IL-1) production by monocytes; wherein a culture condition suitable for expressing the polypeptide is selected and the polypeptide is isolated from the culture;

(2) A process for making an apo-A-1 fragment T-cell activation inhibitor-like polypeptide fragment comprising culturing a prokaryotic cell comprising a vector comprising a nucleic acid molecule consisting of the nucleotide sequence selected from the group consisting of: (a) the

nucleotide sequence as set forth in residues 73 to 582 in SEQ ID NO: 1; (b) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 194 in SEQ ID NO: 2; (c) the nucleotide sequence as set forth in residues 73 to 432 in SEQ ID NO:1; (d) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 144 in SEQ ID NO22; (e) the nucleotide sequence as set forth in residues 466 to 801 in SEQ l D NO:1; (f) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 11 3 in SEQ ID NO:2; (g) a nucleotide sequence encoding the polypeptide as set forth in residues 73 to 113 in SEQ ID NO:2; (h) a nucleotide sequence encoding the polypeptide as set forth in residues 156 to 267 in SEQ ID NO:2 wherein the polypeptide inhibits tumor necrosis factor (TNF) or interleukin-1 (IL-1) production by monocytes; wherein a culture condition suitable for expressing the polypeptide is selected and the polypeptide is isolated from the culture;

(3) An isolated apo-A-l fragment T-cell activation inhibitor-like polypeptide fragment consisting of the amino acid sequence selected from the group consisting of: (a) an amino acid sequence as set forth in residues 25 to 194 of SEQ ID NO: 2; (b) an amino acid sequence as set forth in residues 25 to 144 of SEQ ID NO: 2; (c) an amino acid sequence as set forth in residues 156 to 267 of SEQ ID NO: 2; (d) an amino acid sequence as set forth in residues 25 to 113 of SEQ ID NO: 2; (e) an amino acid sequence as set forth in residues 73 to 113 of SEQ ID NO: 2 and wherein the polypeptide inhibits tumor necrosis factor (TNF) or interleukin-l (IL-1) production by monocytes;

(4) An isolated apo-A-l fragment T-cell activation inhibitor-like polypeptide fragment encoded by a nucleic acid molecule consisting of the nucleotide sequence selected from: (1) the nucleotide sequence as set forth in residues 73 to 582 in SEQ ID NO: 1; (2) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 194 in SEQ ID NO: 2; (3) the nucleotide sequence as set forth in residues 73 to 432 in SEQ ID NO: 1; (4) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 144 in SEQ ID NO:2; (5) the nucleotide sequence as set forth in residues 466 to 801 in SEQ ID NO: 1; (6) a nucleotide sequence encoding the polypeptide as set forth in residues 25 to 113 in SEQ ID NO: 2; (7) a nucleotide sequence encoding the polypeptide as set forth in residues 73 to 113 in SEQ ID NO: 2; (8) a nucleotide sequence encoding the polypeptide as set forth in residues 156 to 267 in SEQ ID NO: 2 wherein the nucleotide sequence encodes a polypeptide that inhibits tumor necrosis factor (TNF) or interleukin-l (IL-1) production by monocytes;

(5) A composition comprising the polypeptide mentioned above and a pharmaceutically acceptable formulation agent;

(6) A composition comprising the polypeptide mentioned above and a pharmaceutically acceptable formulation agent wherein the pharmaceutically acceptable formulation agent comprises at least one of a carrier, adjuvant, solubilizer, stabilizer, or anti-oxidant;

(7) The isolated mentioned above which is covalently modified with a water-soluble polymer;

(8) The isolated polypeptide mentioned above wherein the water-soluble polymer is selected from polyethylene glycol, monomethoxy-polyethylene glycol, dextran, cellulose, poly-tN-vinyl pyrrolidone) polyethylene glycol, propylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols, and polyvinyl alcohol;

(9) A fusion polypeptide comprising the isolated apo-A-l fragment T-cell activation inhibitor-like polypeptide fragment mentioned above and a heterologous amino acid sequence selected from an IgG constant domain or fragment thereof, an alkaline phosphatase or a fragment thereof, a tat protein, or a FLAG epitope and

(10) The fusion polypeptide mentioned above and a heterologous amino acid sequence wherein the heterologous amino acid sequence is an IgG constant domain for detection assays. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation. This rejection encompasses three distinct issues, which will be addressed in turn:

(a) Enablement is not commensurate in scope with claims as how to make any apo-A-1 fragment T-cell activation inhibitor-like polypeptide fragment using the nucleotide sequence "complementary " to any of the nucleotide sequence as set forth in claims 9(i) and 10(i).

The nature of the invention is the process for making the apo-A1 fragment T-cell activation inhibitor-like polypeptide (AFTI) polypeptides in either eukaryotic cell using any complement (antisense) nucleic acid sequence of the nucleotide encoding the apo-A1 fragment T-cell activation inhibitor-like polypeptide. In order to make and use the claimed invention, one has to be in possession of the nucleotide encoding the AFTI polypeptides. In order to make the polypeptide, one has to use the coding strain (sense) of the polynucleotide encoding the claimed AFTI polypeptide to express the polypeptide.

The specification discloses only the use of *coding region* of polynucleotide encoding AFTI polypeptide in a plasmid to produce the claimed polypeptide (se page 79, line 11).

The specification does not teach the use of the complement, the antisense or the non-coding strain to make the claimed polypeptide. One cannot extrapolate the teachings of the specification to the scope of the claims because the process claims are drawn to polypeptide that is encoded by a complementary (antisense) sequence to nucleotide sequence as set for in residues 73 to 582 in SEQ ID NO: 1, or residues 73 to 432 in SEQ ID NO: 1, or residues 466 to 801 in SEQ ID NO: 1, or which is not the AFTI polypeptide as set forth in residues 25 to 194 in SEQ ID NO: 2, residues 25 to 144 in SEQ ID NO: 2, residues 25 to 113 in SEQ ID NO: 2, residues 73 to 113 in SEQ ID NO: 2 and residues 156 to 267 in SEQ ID NO: 2, respectively. The complementary sequence of the nucleic acid encoding SEQ ID NO: 1 has no open reading frame (ORF) for AFTI polypeptide. The resultant polypeptides made by the claimed process do not have the biological properties representative of what is being claimed, and the specification has not enabled any of these types of polypeptides because it has not been shown that these polypeptides are capable of functioning as that which is being disclosed. There are no working examples of such polypeptide made by such process. The specification provides no guidance on this point. Accordingly, an undue amount of experimentation would be required to determine how to practice the invention using the complement (antisense) nucleotide sequence to make AFTI polypeptide fragment that has the properties of inhibiting tumor necrosis factor (TNF) or interleukin-1 (IL-1) production by monocytes, let alone the polypeptides having the same structure as set forth in claims 9 and 10.

(b) Enablement is not commensurate in scope with claims as how to make and use any apo-A-1 fragment T-cell activation inhibitor-like polypeptide fragment (AFTI) having "one or more conservative amino acid substitutions" as set forth in claims 9(j), 10(i), 15(f), and 16.

The claims encompass any nucleotide sequence encoding any AFTI polypeptide in residues 73 to 582 in SEQ ID NO: 1, or residues 73 to 432 in SEQ ID NO: 1, or residues 466 to 801 in SEQ ID NO: 1, having any "one or more conservative amino acid substitutions" or any isolated apo-A-1 fragment T-cell activation inhibitor-like polypeptide fragment (AFTI) encoded by the nucleotide sequence set forth in claim 16 having any "one or more conservative amino acid substitutions".

The specification discloses only human Apo-A-I comprising SEQ ID NO: 2 encoding by the polynucleotide of SEQ ID NO: 1. The only human Apo-A1 fragment recovering from the fractions 23-26 with a molecular weight 28 kDa protein consisting of amino acid residues 25 to 194 of SEQ ID NO: 2 has inhibitory activity of T cell signaling of monocyte for IL-1β and TNFα production in vitro (See p7, Figure 4A-B). The term conservative amino acid substitution" as defined in the specification at page 25 is any substitution of a native amino acid residue with a nonnative residue, including non-naturally occurring amino acid residues exemplified in Table 1.

The specification does not teach which amino acids within the full-length sequence of human Apo-A-I polypeptide (AFTI) are critical and can or cannot be change such as substitution, deletion, addition and combination thereof. The specification does not teach any assays that is useful for screening variants and is predictive of success in vivo. There is no disclosure of any apo-A-1 fragment T-cell activation inhibitor-like polypeptide fragment (AFTI) having more than one conservative amino acid substitutions, much less the radically different polypeptides having no resemblance to amino acid residues 25 to 194 of SEQ ID NO: 2 still maintain structure and functions. Therefore, the only isolated apo-A-l fragment T-cell activation inhibitor-like polypeptide fragment (AFTI) that are enabled are those consisting of the amino acid sequence as set forth in residues 25 to 194 of SEQ ID NO: 2; (b) an amino acid sequence as set forth in residues 25 to 144 of SEQ ID NO: 2; (c) an amino acid sequence as set forth in residues 156 to 267 of SEQ ID NO: 2; (d) an amino acid sequence as set forth in residues 25 to 113 of SEQ ID NO:2; (e) an amino acid sequence as set forth in residues 73 to 1 13 of SEQ ID NO22, the corresponding polynucleotide encoding said polypeptides. It is not predictable which undisclosed AFTI having more than one conservative amino acid substitutions inhibits tumor necrosis factor production or interleukin-1 (IL-1) production, or T cell activation. There are no working examples of such (AFTI) polypeptide. The state of the art is such that even a single amino acid substitution in a protein leads to unpredictable changes in the biological activity of the protein.

Mason *et al* (Molecular Endocrinology 8(3): 325-332, 1994; PTO 892) teach in activin A, even a single amino acid substitution from cysteine to alanine fails to maintain either the structure and/or functions such as intracellular assembly and secretion of the dimer protein (see page 327, column 1, in particular), loss biological activity (See activin cysteine mutant 4 and 12, page 327, column 2, in particular) and loss of receptor binding activity (See Receptor Binding Activities of activin cysteine mutant 4 and 12, page 327, column 2, in particular). Mason *et al* further teach an equivalent protein such as TGFβ1 in which replacing cysteine residue for a serine residue resulted in loss bioactivity (See page 330, column 1, first paragraph, in particular).

Mikayama *et al*, of record, teach that the human glycosylation-inhibiting factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (Figure 1 in particular). Yet, Mikayama *et al*, of record, teach further that GIF is unable to carry out the function of MIF and MIF does not demonstrate GIF bioactivity (Abstract in particular). It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell.

Attwood *et al*, of record, teach that protein function is context-dependent and the state of the art of making functional assignments merely on the basis of some degree of similarity between sequences and the current structure prediction methods is unreliable.

Skolnick *et al*, of record, teach that squence-based methods for function prediction are inadequate and knowing a protein's structure does not necessary tell one it's function (See entire document, Abstract in particular). While it is known in the art how to make amino acid substitution in polypeptide, such polypeptide is not predictable of their being able to inhibit TNF or IL-1 production in vivo or T cell activation. Therefore, it would require undue experimentation to determine how to practice the invention as it is drawn to any apo-A-1 fragment T-cell activation inhibitor-like polypeptide fragment (AFTI) having no resemblance to the residues 25 to 194 of SEQ ID NO: 2, the corresponding polynucleotide other than those specific nucleic acid sequences consisting of the (nucleotides 73 to 582, 73 to 432, 466 to 801 in SEQ ID NO: 1) and amino acid sequences consisting of the (residues 25 to 194, 25 to 144, 25 to 113, 73 to 113 and 156 to 267 in SEQ ID NO: 2). Given the unlimited number of apo-A-I fragment T-cell activation inhibitor-like polypeptide fragment having one or more substitutions, the radically different polypeptides would obviously be inoperable. Accordingly, an undue experimentation would be required to determine how to practice the claimed invention.

(C) Enablement is not commensurate in scope with claims as how to make and use any apo-A-1 fragment T-cell activation inhibitor-like polypeptide fragment (AFTI) encoded by any nucleic acid molecule *consisting essentially of* any nucleotide sequence as set forth in claims 9-10, 15-16, 36-43 and 46-49. In order to make and use the claimed invention, one has to be in possession of the nucleic acid sequence or the corresponding amino acid sequence of apo-A-1 fragment T-cell activation inhibitor-like polypeptide fragment (AFTI) that inhibit TNF or IL-1 production by monocytes.

In addition to the problems mentioned above, there is insufficient guidance as to the structure of any AFTI-like polypeptide without the nucleotide sequence or the amino acid sequence. The term "consisting essentially of" is open-ended. It expands the nucleic acid sequence from (nucleotides 73 to 582, 73 to 432, 466 to 801 in SEQ ID NO: 1) and amino acid sequences from (residues 25 to 194, 25 to 144, 25 to 113, 73 to 113 and 156 to 267 in SEQ ID NO: 2) to include additional nucleotides, the corresponding amino acids at either or both ends. There is insufficient guidance as to which nucleotides, the corresponding amino acids to be added and whether the resulting AFTI-like polypeptides maintain its structure and functions.

The specification does not teach which amino acids within the full-length sequence of human Apo-A-I polypeptide (AFTI) are critical and can or cannot be change such as substitution, deletion, addition and combination thereof. The specification does not teach any assays that is useful for screening variants and is predictive of success in vivo.

The specification discloses only nucleic acid consisting of (nucleotides 73 to 582, 73 to 432, 466 to 801 in SEQ ID NO: 1) and the amino acid sequences consisting of (residues 25 to 194, 25 to 144, 25 to 113, 73 to 113 and 156 to 267 in SEQ ID NO: 2) inhibits TNF or IL-1 production by monocytes in vitro. There is no disclosure of any polypeptide longer than SEQ ID NO: 2 or any polynucleotide longer than SEQ ID NO: 1. There are no working examples of such polynucleotide and polypeptide inhibiting T cell signaling, TNF or IL-1 production by monocytes in vitro or in vivo.

The state of the art with respect to the issue of structure-function relationship on the ability of apo-A1 to suppress TNF alpha/IL-1 production by monocytes and/or T cell activation is not well understood but may appear that the inhibitory effect of apo-A-1 via T-cell signaling since contact between monocytes and activated T cells was required (see Hyka et al, Immunobiology 97(8): 2381-2389, April 2001, PTO 892; page 2386-87, in particular). The specification provides no guidance as to other apo-A-I polypeptide variants from human or other

species having the same functions as the specific apo-A1 fragment for inhibiting TNF alpha/IL-1 production by monocytes. As such, an undue amount of experimentation would be required to determine how to practice the claimed invention. Given that the interaction between Apo-I polypeptide fragments and monocytes has not been characterized, it would require undue experimentation to determine how to make functional Apo-A1 fragment as broadly as claimed. Since the structures associated with function of any of the apop-A-fragment T-cell activation inhibitor-like polypeptides mentioned above are not enabled, it follows that any composition comprising said polypeptides are not enabled. It also follows that any apop-A-fragment T-cell activation inhibitor-like polypeptides mentioned above covalently modified and any fusion protein comprising said polypeptide are not enabled.

For these reasons, it would require undue experimentation even for one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

6. Claims 9-10, 15-16, 36-43 and 46-49 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification does not reasonably provide a **written description** of (1) a process of making any apo-A-1 fragment T-cell activation inhibitor-like polypeptide fragment using the nucleotide sequence "complementary " to any of the nucleotide sequence as set forth in claims 9(i) and 10(i), (2) any apo-A-I fragment T-cell activation inhibitor-like polypeptide *consisting essentially of* any amino acid sequence from (residues 25 to 194, 25 to 144, 25 to 113, 73 to 113 and 156 to 267 in SEQ ID NO: 2) encoded by any nucleotide sequence (nucleotides 73 to 582, 73 to 432, 466 to 801 in SEQ ID NO: 1) wherein the polypeptide inhibits tumor necrosis factor (TNF) or interleukin-1 (IL-1) production by monocytes as set forth in claims 9-10, 15-16, 36-43

and 46-49, (3) any apo-A-I fragment T-cell activation inhibitor-like polypeptide *consisting essentially of* any amino acid sequence (residues 25 to 194, 25 to 144, 25 to 113, 73 to 113 and 156 to 267 in SEQ ID NO: 2) encoded by any nucleotide sequence (nucleotides 73 to 582, 73 to 432, 466 to 801 in SEQ ID NO: 1) wherein the polypeptide inhibits tumor necrosis factor (TNF) or interleukin-1 (IL-1) having *one more conservative amino acid substitutions*, wherein the polypeptide inhibits tumor necrosis factor (TNF) or interleukin-1 (IL-1) production by monocytes as set forth in claims 9-10, 15-16, 36-43 and 46-49.

The specification discloses only human Apo-A-I comprising SEQ ID NO: 2 encoding by the polynucleotide of SEQ ID NO: 1. The only human Apo-A1 fragment (ATFI) recovering from the fractions 23-26 with a molecular weight 28 kDa protein consisting of amino acid residues 25 to 194 of SEQ ID NO: 2 has inhibitory activity of T cell signaling of monocyte for IL-1β and TNFα production in vitro (See p7, Figure 4A-B).

With the exception of the specific apo-A-1 fragment T-cell activation inhibitor-like polypeptide fragment encoded by nucleic acid sequence consisting of (nucleotides 73 to 582, 73 to 432, 466 to 801 in SEQ ID NO: 1) or the corresponding amino acid sequences consisting of (residues 25 to 194, 25 to 144, 25 to 113, 73 to 113 or 156 to 267 in SEQ ID NO: 2) that inhibit TNF or IL-1 production by monocytes in vitro, there is insufficient written description about the structure associated with function of any apo-A-1 fragment T-cell activation inhibitor-like polypeptide fragment having one or more amino acid substitutions without the amino acid sequence, the corresponding nucleotide sequence. The specification does not describe which amino acids within the full-length sequence of human Apo-A-I polypeptide (AFTI) of SEQ ID NO: 2 or the nucleotides within the nucleic acid sequence of SEQ ID NO: 1 are critical for inhibition of TNF production or IL-1 production by monocytes and can or cannot be change such as substitution, deletion, addition and combination thereof. Given the unlimited number of amino acid substitutions in apo-A-I fragment T-cell activation inhibitor-like polypeptide fragment of (residues 25 to 194, 25 to 144, 25 to 113, 73 to 113 and 156 to 267 in SEQ ID NO: 2), the structures of such radically different polypeptides are not adequately described; the corresponding nucleotides are also not adequately described.

Further, the term "consisting essentially of" is open-ended. It expands the apo-A-I fragment T-cell activation inhibitor-like polypeptide fragment such as amino acid sequences of (residues 25 to 194, 25 to 144, 25 to 113, 73 to 113 and 156 to 267 in SEQ ID NO: 2) and nucleic acid sequence of (nucleotides 73 to 582, 73 to 432, 466 to 801 in SEQ ID NO: 1) to include

additional amino acids and/or nucleotides at either or both ends. The specification does not provide support for which amino acids or corresponding nucleotide to be added such that it maintains its structure and functions, i.e., inhibits TNF or IL-1 production by monocyte. There is no written description of either amino acid sequence or nucleic acid for any such polypeptide larger than SEQ ID NO: 2 or polynucleotide of SEQ ID NO: 1.

With respect to the process of making any apo-A-1 fragment T-cell activation inhibitor-like polypeptide fragment using the nucleotide sequence "complementary " to any of the nucleotide sequence as set forth in claims 9(i) and 10(i), the specification discloses the use of a polynucleotide that encodes the apo-A-I fragment T-cell activation inhibitor-like polypeptide fragment. The use of the *complement* to any nucleotide sequence as set forth in claims 9(i) and 10(i) is not adequate described. This is because translation of the "complementary (antisense) nucleotide sequence to at least one of (a)-(h) does not encode the apo-A-I fragment T-cell activation inhibitor-like polypeptide fragment.

The specification discloses only human apo-A-I fragment T-cell activation inhibitor-like polypeptide fragment (AFTI) consisting of (residues 25 to 194, 25 to 144, 25 to 113, 73 to 113 and 156 to 267 in SEQ ID NO: 2) and nucleic acid sequence consisting of (nucleotides 73 to 582, 73 to 432, 466 to 801 in SEQ ID NO: 1), one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species of polypeptide and polynucleotide to describe the genus. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and Co. 43 USPQ2d 1398; University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC2004).*

Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

8. Claims 9-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "process of making an apo-A-1 fragment ...nucleotide sequence *complementary* to at least one of (a)-(h)..." in claims 9(i) and 10(i) is indefinite and ambiguous because the translation of the "complementary (antisense) nucleotide sequence to at least one of (a)-(h) does not encode the apo-A-I fragment T-cell activation inhibitor-like polypeptide fragment. One of ordinary skill in the art cannot appraise the metes and bound of the claimed invention.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 9-10, 15-16, and 36-39 are rejected under 35 U.S.C. 102(b) as being anticipated by 5,408,038 (of record, issued April 18, 1995; PTO 892).

The '038 patent teaches an isolated polypeptide apo-A-I consisting essentially the amino acid sequence that is 100% identical to the claimed SEQ ID NO: 2 (see reference SEQ ID NO: 3, Fig 2, in particular). The reference polypeptide of SEQ ID NO: 3 encompasses the claimed polypeptide consisting essentially of the amino acid residues (residues 25 to 194, 25 to 144, 25 to 113, 73 to 113 and 156 to 267 in SEQ ID NO: 2). The term "consisting essentially of" is open-ended. It expands the claimed fragment to include additional amino acids at either or both ends to include the reference polypeptide. Given that the reference polypeptide has the same structure as the claimed apo-A-I polypeptide, the reference polypeptide inherently has the same properties such as inhibition of tumor necrosis or interleukin-1 (IL-1) production by monocytes. The '038 patent teaches one or more conservative amino acid substitutions (see col. 10, lines 1 to 40, col. 19, line 65-68 bridging col. 20, lines 1-11, in particular). The '038 patent also teaches a nucleic acid comprising SED ID NO: 4 that encodes the claimed apo-A-I polypeptide of SEQ ID NO: 2. The reference nucleotide sequence of SEQ ID NO: 4 includes the claimed (nucleotides 73 to 582, 73 to 432, 466 to 801 in claimed SEQ ID NO: 1). Again, the term "consisting essentially of" is open-ended. It expands the claimed fragment to include additional nucleotides at either or both ends to include the reference nucleotide sequence. The '038 patent further teaches a process of making the reference polypeptide comprising culturing a eukaryotic cell comprising vector having the DNA encoding the reference polypeptide (see col. 31, lines 45-58, col. 30, lines 21-26, in particular). The '038 patent further teaches a fusion protein comprising the reference apo A-I

polypeptide from residue 19 through residue 240 fused to a heterologous amino acid sequence such as β-galactosidase (see col. 18, lines 22-25, claim 12 of the '038 patent in particular). The '038 patent also teaches a composition comprising the reference apo-A-I polypeptide and a carrier such as phosphate-buffered saline or solubilizer such as triton X-100 (see col. 12, lines 62-67, in particular). Thus, the reference teachings anticipate the claimed invention.

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

13. Claims 15-16 and 36-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over 5,408,038 (of record, issued April 18, 1995; PTO 892) in view of US Pat No. 5,824,784 (Oct 1998; PTO 892) and/or US Pat No. 5,876,968 (issued March 2, 1999; PTO 892).

The teachings of the '038 patent have been discussed supra. The '038 patent teaches apoA-I is unstable (see column 2, lines 6-8, in particular). The '038 patent teaches the reference apo-A-I is useful for diagnostic assays for determining HDL and LDL levels in body fluid sample (see abstract, in particular).

The claimed invention in claims 38, and 39 differs from the teachings of the reference only in that composition wherein the pharmaceutically acceptable formulation agent comprises at least one of adjuvant, stabilizer or anti-oxidant.

The claimed invention as recited in claims 40 and 42 differs from the teachings of the reference only in that polypeptide is covalently modified with a water-soluble polymer.

The claimed invention as recited in claims 41 and 43 differs from the teachings of the reference only in that polypeptide is covalently modified with a water soluble polymer wherein the water soluble polymer is selected from polyethylene glycol, monomethoxy polyethylene glycol, dextran, cellulose, poly(N-vinyl pyrrolidone) polyethylene glycol, propylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols and polyvinyl alcohol.

The '784 patent teaches method and composition for covalently modified any polypeptide of interest such as G-CSF or INF with a water-soluble polymer such as polyethylene glycol, monomethoxy polyethylene glycol, dextran, cellulose, poly(N-vinyl pyrrolidone) polyethylene glycol, propylene glycol homopolymers, polypropylene oxide/ethylene oxide co-polymers, polyoxyethylated polyols and polyvinyl alcohol (See abstract, column 6, lines 32-67 bridging column 7, lines 1-5, column 9, lines 64-66, in particular). The '784 patent further teaches pharmaceutically acceptable formulation agent such as carrier such as phosphate buffer, adjuvant, solubilizer such as Tween 80, anti-oxidants such as ascorbic acid, and sodium metafisulfate (See column 11, lines 11-32, in particular). The advantages of N-terminally pegsylated protein are that it provides a homogeneous preparation to ease in clinical application, with predictability of lot to lot pharmacokinetics for desired dosage, increasing circulation time such as sustained release and resistance to proteolysis and other consideration such as lack of antigenicity (See column 5, lines 29-35, column 6, lines 44-48, column 7, lines 1-5, in particular).

The '968 patent teaches a pharmaceutical composition comprising human Apo A1-M together with a stabilizing agent such as phospholipids and/or a carrier (see paragraph bridging col. 3 and col. 4, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to covalently modified the apo-A-I polypeptide as taught by the '038 patent to the water soluble polymer as taught by the '784 patent and formulates the composition in pharmaceutically acceptable carrier such as phosphate buffer, solubilizer such as Tween 80 or stabilizer or antioxidant as taught by the '784 patent and/or the phospholipids stabilizer as taught by the '968 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '038 patent teaches that apoA-I is unstable (see column 2, lines 6-8, in particular) and the apo-A-I

polypeptide is useful for diagnostic assays for determining HDL and LDL levels in body fluid sample (see abstract, in particular). The advantages of N-terminally pegsylated protein are that it provides a homogeneous preparation to ease in clinical application, with predictability of lot to lot pharmacokinetics for desired dosage, increasing circulation time such as sustained release and resistance to proteolysis and other consideration such as lack of antigenicity as taught by the '784 patent (See column 5, lines 29-35, column 6, lines 44-48, column 7, lines 1-5, in particular). The '968 patent teaches a pharmaceutical composition comprising human Apo A1-M together with a stabilizing agent such as phospholipids and/or a carrier (see paragraph bridging col. 3 and col. 4, in particular).

14. Claims 15-16 and 46-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over 5,408,038 (of record, issued April 18, 1995; PTO 892) in view of US Pat 5,116,964 (of record, May 1992; PTO 892).

The teachings of the '038 patent have been discussed supra. The '038 patent further teaches a fusion protein comprising the reference apo A-I polypeptide from residue 19 through residue 240 fused to a heterologous amino acid sequence such as β-galactosidase (see col. 18, lines 22-25, claim 12 of the '038 patent in particular). The '038 patent teaches the reference apo-A-I is useful for diagnostic assays for determining HDL and LDL levels in body fluid sample (see abstract, in particular).

The claimed invention as recited in claims 46-49 differs from the teachings of the reference only that the fusion polypeptide comprising an isolated apo-A-I T cell activation inhibitor-like polypeptide fragment consisting essentially of an amino acid sequence as set forth in (a) to (e) having one or more conservative amino acid substitutions fused to an IgG constant or fragment thereof instead of β-galactosidase.

The '964 patent teaches immunoglobulin fusion polypeptide comprising a fragment of immunoglobulin such as CH2 and CH3 domains of the constant region of an immunoglobulin or the Fc fused to any polypeptide of interest such as LHR (See abstract, column 10, lines 10-16, in particular). The advantage of immunoglobulin fusion polypeptide is that it extends the half-lives of the fusion protein and is useful in therapeutic or diagnostic (See column 8, lines 10-34, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the β-galactosidase in the fusion protein comprising apo A-I

polypeptide fused to β-galactosidase as taught by the '038 patent for the CH2 and CH3 domains of the constant region of an immunoglobulin or the Fc as taught by the '964 patent. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '038 patent teaches that apoA-I is unstable (see column 2, lines 6-8, in particular) and the '964 patent teaches immunoglobulin fusion polypeptide extends the half-lives of the fusion protein (See column 8, lines 10-34, in particular).

15. Claims 15-16, 46 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over 5,408,038 (of record, issued April 18, 1995; PTO 892) in view of Schwarze et al (Science 285(3): 1569-1572, Sept 1999; PTO 892) or US Pat No 5,789,655 (issued Aug 4, 1998; PTO 892) or Kershbaumer et al (Immunotechnology 2(2): 145-50, June 1996; PTO 892).

The teachings of the '038 patent have been discussed supra. The '038 patent further teaches a fusion protein comprising the reference apo A-I polypeptide from residue 19 through residue 240 fused to a heterologous amino acid sequence such as β-galactosidase (see col. 18, lines 22-25, claim 12 of the '038 patent in particular). The '038 patent teaches the reference apo-A-I is useful for diagnostic assays for determining HDL and LDL levels in body fluid sample (see abstract, in particular).

The claimed invention as recited in claims 46 and 48 differs from the teachings of the reference only in that the fusion polypeptide wherein the heterologous amino acid sequence is an alkaline phosphatase, a tat protein, or a FLAG epitope.

Schwarze et al teach a fusion protein comprising a tat protein containing an NH-2 terminal 11 amino acid protein transduction domain (PTD) fused to β-gal (see page 1569 to 1570, Fig 2A, in particular) or FITC (see page 1570, in particular). Schwarze et al teach the tat protein in the fusion protein is useful for delivering the fusion protein inside the cells of the patients in the context of protein therapy (see page 1571, col. 1, abstract, in particular).

The '655 patent teaches various epitope sequences such as FLAG epitope that are useful for tagging and detecting recombinant proteins (see col. 11, lines 50-67, col. 12, lines 1-9, in particular). The '655 patent teaches inclusion of the FLAG epitope in the recombinant fusion

proteins avoids the necessity for the development of a specialized scheme or functional assays for protein purification (se col. 12, lines 5-10, in particular).

Kershbaumer et al teach alkaline phosphatase fusion proteins comprising single chain Fv fragments fused to the N-terminus of alkaline phosphatase from E coli (see abstract, in particular). The fusion protein is useful in single step purification via metal affinity chromatography for various assays such as ELISA and immunowestern blotting (see abstract, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the β-galactosidase in the fusion protein comprising apo A-I polypeptide having one or more conservative amino acid substitution fused to β-galactosidase as taught by the '038 patent for the tat protein that deliver the protein inside the cell as taught by Schwarze or the FLAG epitope as taught by the '655 patent, or the alkaline phosphatase as taught by Kershbaumer et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because the '038 patent teaches the reference apo-A-I is useful for diagnostic assays for determining HDL and LDL levels in body fluid sample (see abstract, in particular). Schwarze et al teach the tat protein in the fusion protein is useful for delivering the fusion protein inside the cells in the context of protein therapy (see page 1571, col. 1, abstract, in particular). The '655 patent teaches FLAG epitope fusion protein is useful for tagging and detecting recombinant proteins and avoids the necessity for the development of a specialized scheme or functional assays for protein purification (se col. 12, lines 5-10, in particular). Kershbaumer et al teach alkaline phosphatase in the fusion protein is useful in single step purification via metal affinity chromatography for various assays such as ELISA and immunowestern blotting (see abstract, in particular).

16. No claim is allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Friday from 9:00 am to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone

are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

18. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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